14

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
B0046WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/09137	18/09/2000	16/09/1999
International Patent Classification (IPC) or national classification and IPC C07K14/705		
Applicant WARNER-LAMBERT COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 16 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/02/2001	07.12.2001
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Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09137

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-8,10-46	as originally filed			
9	as received on	19/09/2001	with letter of	14/09/2001

Claims, No.:

1-15,27-53	as originally filed			
16-26	as received on	19/09/2001	with letter of	14/09/2001

Drawings, sheets:

1/2,2/2	as originally filed

Sequence listing part of the description, pages:

1-106, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☒ contained in the international application in written form.
   - ☒ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☒ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule

68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4, 8, 9, 12, 14, 20-29, 42, 48, 53
	No:	Claims	1-3, 5-7, 10-11, 13, 15-19, 30-41, 43-47, 49-52
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-53
Industrial applicability (IA)	Yes:	Claims	1-53
	No:	Claims	

2. Citations and explanations
   see separate sheet

Reference is made to the following documents:

D1: BROWN J P ET AL: 'CLONING AND DELETION MUTAGENESIS OF THE ALPHA 2 DELTA CALCIUM CHANNEL SUBUNIT FROM PORCINE CEREBRAL CORTEX' JOURNAL OF BIOLOGICAL CHEMISTRY,US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 273, no. 39, 1998, pages 25458-25465, XP000887190 ISSN: 0021-9258

D2: KLUGBAUER N ET AL: 'MOLECULAR DIVERSITY OF THE CALCIUM CHANNEL ALPHA 2 DELTA SUBUNIT' JOURNAL OF NEUROSCIENCE,US,NEW YORK, NY, vol. 19, no. 2, 15 January 1999 (1999-01-15), pages 684-691, XP000886459 ISSN: 0270-6474

D3: WILLIAMS M E ET AL: 'STRUCTURE AND FUNCTIONAL EXPRESSION OF ALPHA1, ALPHA2, AND BETA SUBUNITS OF A NOVEL HUMAN NEURONAL CALCIUM CHANNEL SUBTYPE' NEURON,US,CAMBRIDGE, MA, vol. 8, January 1992 (1992-01), pages 71-84, XP000886416

D4: WO 00 20450 A (WARNER LAMBERT CO ;MOLDOVER BRIAN (US); JOHNS MARGARET ANN (US); O) 13 April 2000 (2000-04-13)

1. The corrections of obvious errors submitted with letter dated 14.09.2001 fulfils the requirements of Rule 91 PCT.

Re Item II

Priority

2. The priority document (US09/397,550) does not disclose the sequences

of SEQ IDs 29 to 55. Therefore, the claims referring back to said SEQ IDs are not entitled to the claimed priority. Said claims correspond to the inventions 3 to 5.

Re Item IV

Lack of unity of invention

3.1 The International Search Report has been drawn up in respect of the entire international application. In accordance with the ISA, the IPEA finds that the application does not comply with the requirement of unity of invention (Article 34(3) and Rules 13 and 68 PCT).

3.2 The application is considered to lack unity of invention since its subject-atter relates not to one but rather to five separate inventions not linked together by a common underlying inventive concept. The claims and the inventions to which they relate may be grouped as follows:

1. Claims 1 to 20 (in part), 21 to 23, 35 to 53 (in part)
Soluble calcium channel alpha2delta subunits deriving or originating from a polypeptide having the amino acid sequence of SEQ ID N° 20 (including the derivates having sequences as set forth in SEQ ID N° 4-6) and related subject-matter.

2. Claims 1 to 20 (in part), 24 to 26, 35 to 53 (in part)
Soluble calcium channel alpha2delta subunits deriving or originating from a polypeptide having the amino acid sequence of SEQ ID N° 22 (including the derivates having sequences as set forth in SEQ ID N° 10-12) and related subject-matter.

3. Claims 1 to 20 (in part), 27 to 29, 35 to 53 (in part)
Soluble calcium channel alpha2delta subunits deriving or originating from a polypeptide having the amino acid sequence of SEQ ID N° 53-55 and related subject-matter.

4. Claims 1 to 20 (in part), 30 to 53 (in part)
Soluble calcium channel alpha2delta subunit deriving or originating from a polypeptide having the amino acid sequence of SEQ ID 44 (including the derivates having sequences as set forth in SEQ ID N° 41-43) and related subject-matter.

5. Claims 1 to 20 (in part), 30 to 53 (in part)
Soluble calcium channel alpha2delta subunit deriving or originating from a polypeptide having the amino acid sequence of SEQ ID N° 33 (including the derivates having sequence as set forth in SEQ ID N° 34-36) and related subject-matter.

3.3 An international application must relate to one invention or to a group of inventions so linked as to form a single general inventive concept. Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features. Special technical features are such features that define the contribution of the claimed invention over the prior art.

The identified five inventions relate to modified calcium channel alpha2delta subunits which involve the technical feature of being soluble and of retaining the functional characteristics of the full-length or wild type calcium channel alpha2delta subunits from which they derived as the sole common link. However, this feature cannot be accepted to constitute a special technical feature because it does not define a contribution over the prior art (see D1, the abstract and the paragraph bridging the left and right hand columns page 2546).

Therefore the IPEA is of the opinion that there is no single unifying inventive concept underlying the entire group of claims of the present application as required by Rule 13 PCT.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4. **INVENTION N°1**

Claims 1 to 20 (in part), 21 to 23, 35 to 53 (in part).
Soluble calcium channel alpha2delta subunits deriving or originating from a polypeptide having the amino acid sequence of SEQ ID N° 20 (including the derivates having sequences as set forth in SEQ IDs N° 4-6) and related subject- matter.

The subject-matter of claim 1 according to the first invention corresponds to the introduction of the subject-matter of claim 21 in claim 1.

The human α2δ-2 protein having the sequence shown in SEQ ID N° 20 is known from the prior art (see D2 Figure 1 page 685).
Said human α2δ-2 protein of D2 is considered to represent the most relevant state of the art.
The difference between said protein and the subject-matter of claim 1 is that the human α2δ-2 protein of D2 is not soluble.
The problem to be solved by the present invention may therefore be regarded as the obtention of a soluble α2δ–2 polypeptide deriving from the human α2δ-2 protein of D2 and retaining the activity of the wild-type protein.
Claim 1 does not propose any technical solution to said problem since claim 1 is defined by the goal to be achieved.
Therefore claim 1 is not considered to involve an inventive step (Article 33.3 PCT).

The most precise solutions proposed to the above mentioned problem in the first invention of the present application are the solutions of claims 22 and 23.
The solutions of claims 22 and 23 are a polypeptide **comprising** or consisting of the SEQ IDs N°4, 5 or 6 which correspond to three different C-terminal deletions of the protein shown in SEQ ID N°20 and a polypeptide **comprising** or consisting of the region comprised between amino acid number 340 and amino acid number 1062 of SEQ ID N°20,

respectively .

The solution proposed in claims 22 and 23 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

It is known from the prior art that soluble mutants of α2δ–1 subtype can be obtained by deleting the putative membrane anchor in the δ sequence. D1 discloses several truncated mutants of the α2δ–1 calcium channel subunit from porcine cerebral cortex. Truncated mutants L(Δ1040-1067), K(Δ1013-1067) and J(Δ995-1067) retain Gabapentin binding activity and at least the mutant L is soluble (see D1 Fig 2 and the paragraph bridging the left and right hand columns page 25462). Therefore, it is obvious for the person skilled in the art that truncated mutants with deletions corresponding to the deletion of mutant L are very likely to be soluble and to retain binding activity. The position 1039 of the protein of D1 corresponds to the position 1109 in the sequence of SEQ ID N°20, therefore the polypeptide having SEQ ID N°6 which is truncated after position 1109 has the deletion corresponding to the deletion of the mutant L of D1. Said polypeptide also **comprises** the sequences shown in SEQ IDs N°4 and 5 and the region comprised between amino acid number 340 and amino acid number 1062 of SEQ ID N°20. Therefore, the solutions of claims 22 and 23 do not involve an inventive step in view of D1 and D2 (Article 33.3 PCT).

From the above objections, it appears that the α2δ subunits according to claims 1 to 23 and 35 of the first invention do not involve an inventive step (Article 33.3 PCT).

The present authority is also of the opinion that the subject-matter of claims 36 to 53 can only involve an inventive step if the subject matter of claims 1 to 23 and 35, to which they refer directly or indirectly, is novel and involve an inventive step (Article 33.3 PCT).

5. **INVENTION N°2**

Claims 1 to 20 (in part), 24 to 26, 35 to 53 (in part).

Soluble calcium channel alpha2delta subunits deriving or originating from a polypeptide having the amino acid sequence of SEQ ID N° 22

(including the derivates having sequences as set forth in SEQ IDs N° 10-12) and related subject-matter.

The subject-matter of claim 1 according to the 2nd invention correspond to the introduction of the subject-matter of claim 24 in claim 1.

The mouse α2δ-3 protein is known from the prior art (see D2 Figure 1 page 685).
Said mouse α2δ-3 protein of D2 is considered to represent the most relevant sate of the art.
The difference between said protein and the subject-matter of claim 1 is that the protein of D2 is not soluble and is not from human origin.
The problem to be solved by the present invention may therefore be regarded as the obtention of a soluble α2δ–3 polypeptide deriving from the human homolog of the mouse α2δ-3 of D2 and retaining the activity of the wild-type protein.

Claim 1 does not propose any technical solution to said problem since claim 1 is defined by the goal to be achieved.
Therefore claim 1 is not considered to involve an inventive step (Article 33.3 PCT).

The most precise solutions proposed to the above mentioned problem in the 2nd invention of the present application are the solutions of claims 25 and 26.
The solutions of claims 25 and 26 are a polypeptide **comprising** or consisting of the SEQ IDs N°10, 11 or 12 which correspond to three different C-terminal deletions of the protein shown in SEQ ID N°22 and a polypeptide **comprising** or consisting of the region comprised between amino acid number 306 and amino acid number 1019 of SEQ ID N°22 (it appears that claim 26 should make reference to SEQ ID N°22 and not 20), respectively.
The solutions proposed in claims 25 and 26 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

1- The motivation exist in the art to isolate the human homolog of the mouse protein since the ultimate goal is to find compounds useful in human medicine.
Since it is known from D1 that the α2δ-1 subunit is highly conserved between pig, rat and human (see the abstract of D1), the same level of sequence conservation can also be expected between the proteins of α2δ-3 subtype. Consequently, the person skilled in the art willing to isolate the human homolog of the mouse α2δ–3 subunit would expect very high chances of success.
Moreover, it is routine work to isolate highly identical genes using for example PCR based methods or low stringency hybridizations and the isolated gene inherently encodes a protein having the sequence shown in SEQ ID N°22. Therefore the obtention of the sequence shown in SEQ ID N°22 is not considered as involving an inventive step.

2. It is known from the prior art that soluble mutants of the α2δ-1 subtype can be obtained by deleting the putative membrane anchor in the δ sequence. D1 discloses several truncated mutants of the α2δ–1 calcium channel subunit from porcine cerebral cortex. Truncated mutants L(Δ1040-1067), K(Δ1013-1067) and J(Δ995-1067) retain Gabapentin binding activity and at least the mutant L is soluble (see D1 Fig 2 and the paragraph bridging the left and right hand columns page 25462). It is therefore obvious for the person skilled in the art that truncated mutants with deletions corresponding to the deletion of mutant L are very likely to be soluble and to retain binding activity.
The position 1039 of the protein of D1 corresponds to the position 1065 in the sequence of SEQ ID N°22. Therefore, the polypeptide having SEQ ID N°12 which is truncated after position 1065 has the deletion corresponding to the deletion of the mutant L of D1. Said polypeptide also **comprises** the sequence shown in SEQ IDs N°10 and 11 and the region comprised between amino acid number 306 and amino acid number 1019 of SEQ ID N°22. Therefore, the solutions of claims 22 and 23 do not involve an inventive step in

view of D1 and D2 (Article 33.3 PCT).

From the above objections, it appears that the calcium channels according to claims 1 to 20, 24 to 26 and 35 of the 2nd invention do not involve an inventive step (Article 33.3 PCT).

The present authority is also of the opinion that the subject-matter of claims 36 to 53 can only involve an inventive step if the subject matter of claims 1 to 20, 24 to 26 and 35, to which they refer directly or indirectly, is novel and involve an inventive step (Article 33.3 PCT).

6. **INVENTION N°3**

Claims 1 to 20 (in part), 27 to 29, 35 to 53 (in part).
Soluble calcium channel alpha2delta subunits deriving or originating from a polypeptide comprising the amino acid sequence of SEQ ID N° 55 (including the derivates having sequences as set forth in SEQ IDs N°53-55) and related subject- matter.

The subject-matter of claim 1 according to the 3rd invention corresponds to the introduction of the subject-matter of claim 27 in claim 1.

The human α2δ-4 is known from the prior art (see D4 SEQ ID N°6 and the paragraph 2. of the present Written Opinion). The sequence shown in SEQ ID N°55 corresponds to the amino acids 1 to 1096 of the protein of D4 (the sequence of SEQ ID N°55 displays however an additional serine residue in position 748 which corresponds likely to an error either in the sequence of the protein of D4 or in the sequence of SEQ ID N°55).
Said human α2δ-4 protein of D4 is considered to represent the most relevant state of the art.
The difference between said protein and the subject-matter of claim 1 is that the protein of D4 is not soluble.
The problem to be solved by the present invention may therefore be regarded as the obtention of a soluble α2δ-4 polypeptide deriving from the protein of D4 and retaining the binding activity of the wild-type protein.

Claim 1 does not propose any technical solution to said problem since claim 1 is defined by the goal to be achieved.
Therefore, claim 1 is not considered to involve an inventive step (Article 33.3 PCT).

The most precise solutions proposed to the above mentioned problem in the 3rd invention of the present application are the solutions of claims 28 and 29.
The solutions of claim 28 and 29 are a polypeptide **comprising** or consisting of the SEQ IDs N°53, 54 or 55 which correspond to three different C-terminal deletions of the protein of D4 and a polypeptide **comprising** or consisting of the region comprised between amino acid number 302 and amino acid number 1050 of SEQ ID N°55, respectively.
The solutions proposed in claims 28 and 29 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.
It is known from the prior art that soluble mutants of the $\alpha 2\delta$-1 subtype can be obtained by deleting the putative membrane anchor in the δ sequence. D1 discloses several truncated mutants of the $\alpha 2\delta$–1 calcium channel subunit from porcine cerebral cortex. Truncated mutants L(Δ1040-1067), K(Δ1013-1067) and J(Δ995-1067) retain Gabapentin binding activity and at least the mutant L is soluble (see D1 Fig 2 and the paragraph bridging the left and right hand columns page 25462). It is therefore obvious for the person skilled in the art that truncated mutants with deletions corresponding to the deletion of mutant L are very likely to be soluble and to retain binding activity.
The position 1039 of the protein of D1 corresponds to the position 1096 in the sequence of the protein of D4. Therefore, the deletion corresponding to the mutant L of D1 in the protein of D4 corresponds to the polypeptide having the sequence shown in SEQ ID N°55. Said polypeptide also **comprises** the sequences shown in SEQ IDs N°53 and 54, and the region comprised between amino acid number 302 and amino acid number 1050 of SEQ ID N°55. Therefore, the solutions of claims 28 and 29 do not involve an inventive step in view of D1 and D4 (Article 33.3 PCT).

From the above objections, it appears that the calcium channels according to claims 1 to 20, 27 to 29 and 35 of the 3rd invention do not involve an inventive step (Article 33.3 PCT).

The present authority is also of the opinion that the subject-matter of claims 36 to 53 can only involve an inventive step if the subject matter of claims 1 to 20, 27 to 29 and 35, to which they refer directly or indirectly, is novel and involve an inventive step (Article 33.3 PCT).

7. **INVENTION N°4**

Claims 1 to 19 (in part), 30 to 53 (in part).
Soluble calcium channel alpha2delta subunit deriving or originating from a polypeptide having the amino acid sequence of SEQ ID 44 (including the derivates having sequences as set forth in SEQ IDs N° 41-43) and related subject-matter.

The subject-matter of claim 1 according to the 4th invention corresponds to the subject-matter of claim 1 wherein the wild-type α2δ subunit has the amino acid sequence of SEQ ID N°44.

The human α2δ-1 subunit having the sequence shown in SEQ ID N° 44 is known from the prior art (see D3 Figure 3 pages 76 and 77).
Said human α2δ-1 protein of D3 is considered to represent the most relevant state of the art.
The difference between said protein and the subject-matter of claim 1 is that the human α2δ-1 protein of D3 is not soluble.
The problem to be solved by the present invention may therefore be regarded as the obtention of a soluble α2δ–1 polypeptide deriving from the human α2δ-1 protein of D3 and retaining the activity of the wild-type protein.
Claim 1 does not propose any technical solution to said problem since claim 1 is defined by the goal to be achieved.
Therefore, claim 1 is not considered to involve an inventive step (Article

33.3 PCT).

The most precise solutions proposed to the above mentioned problem in the 4th invention of the present application are the solutions of claims 31 and 32.
The solutions of claim 31 and 32 are a polypeptide **comprising** or consisting of the SEQ ID N°41, 42 or 43 which correspond to three different C-terminal deletions of the protein shown in SEQ ID N°44 and a polypeptide **comprising** or consisting of the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°44, respectively .
The solutions proposed in claims 31 and 32 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
It is known from the prior art that soluble mutants of $\alpha 2\delta$–1 subtype can be obtained by deleting the putative membrane anchor in the δ sequence. D1 discloses several truncated mutants of the $\alpha 2\delta$–1 calcium channel subunit from porcine cerebral cortex. Truncated mutants L(Δ1040-1067), K(Δ1013-1067) and J(Δ995-1067) retain Gabapentin binding activity and at least the mutant L is soluble (see D1 Fig 2 and the paragraph bridging the left and right hand columns page 25462). It is therefore obvious for the person skilled in the art that truncated mutants with deletions corresponding to the deletion of mutant L are very likely to be soluble and to retain binding activity. The position 1039 of the protein of D1 corresponds to the position 1063 in the sequence of SEQ ID N°44, therefore the polypeptide having SEQ ID N°43 which is truncated after position 1063 has the deletion corresponding to the deletion of the mutant L of D1. Said polypeptide also **comprises** the sequences shown in SEQ IDs N°43 and 42 and the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°44. Therefore, the solutions of claims 31 and 32 do not involve an inventive step in view of D1 and D3 (Article 33.3 PCT).
From the above objections, it appears that the calcium channels according to claims 1 to 19 and 30 to 35 of the 4th invention do not involve an inventive step (Article 33.3 PCT).

The present authority is also of the opinion that the subject-matter of claims 36 to 53 can only involve an inventive step if the subject matter of claims 1 to 19 and 30 to 35, to which they refer directly or indirectly, is novel and involve an inventive step (Article 33.3 PCT).

8. **INVENTION N°5**

Claims 1 to 3 (in part), 5 to 19 (in part), 30 to 53 (in part).
Soluble calcium channel alpha2delta subunit deriving or originating from a polypeptide having the amino acid sequence of SEQ ID N° 33 (including the derivates having sequence as set forth in SEQ IDs N° 34-36) and related subject- matter.

The subject-matter of claim 1 according to the 5th invention corresponds to the subject-matter of claim 1 wherein the wild-type $\alpha 2\delta$ subunit has the amino acid sequence of SEQ ID N°33.

The pig $\alpha 2\delta$-1 protein having the sequence shown in SEQ ID N° 33 is known from the prior art (see D1 Figure 1 page 25460). D1 discloses several truncated mutants of said protein. Truncated mutants L(Δ1040-1067), K(Δ1013-1067) and J(Δ995-1067) retain Gabapentin binding activity and at least the mutant L is soluble (see D1 Fig 2 and the paragraph bridging the left and right hand columns page 25462). Also disclosed are the corresponding expression vectors and transformed cells (see the Experimental procedure of D1 pages 25460 and 25461). Therefore, D1 is prejudicial to the novelty of claims 1 to 3, 5 to 7, 10, 11, 13, 15 to 19, 30 to 41, 43 to 47 and 49 to 52 (Article 33.2 PCT)
The residual subject-matter namely the subject-matter of claims 8, 9, 12, 14, 42, 48 and 53 is considered to contravene Article 33.3 PCT.

21) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°20.

22) A calcium channel $\alpha_2\delta$ subunit according to 20) or 21) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 4, SEQ ID N° 5 or SEQ ID N° 6.

23) A calcium channel $\alpha_2\delta$ subunit according to any one of 20) to 22) above characterized in that the amino acid sequence of its unprocessed form comprises the region comprised between amino acid number 340 and amino acid number 1062 of SEQ ID N°20.

24) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N° 22.

25) A calcium channel $\alpha_2\delta$ subunit according to 20) or 24) characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 10, SEQ ID N° 11 or SEQ ID N° 12.

26) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 24) or 25) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 306 and amino acid number 1019 of SEQ ID N°20.

27) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°55.

28) A calcium channel $\alpha_2\delta$ subunit according to 20) or 27) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 53, SEQ ID N° 54 or SEQ ID N° 55.

29) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 27) or 28) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1050 of SEQ ID N°55.

30) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°33 or SEQ ID N°44.

31) A calcium channel $\alpha_2\delta$ subunit according to 20) or 30) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 34, SEQ ID N° 35, SEQ ID N° 36, SEQ ID N° 41, SEQ ID N° 42 or SEQ ID N° 43.

from which it originates, said truncation being sufficient to render the truncated δ peptide soluble.

17. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 16 characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the complete α_2 peptide from which it originates.

18. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 15 or 17 characterized in that ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.

19. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 18 characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the complete α_2 peptide from which it originates, its δ peptide comprises at least the ligand-interacting part(s) of the complete δ peptide from which it originates and its δ peptide does not comprise a part of the transmembrane domain of the complete δ peptide from which it originates which renders said calcium channel insoluble.

20. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 19 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates is *$\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4.*

21. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 20 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°20.

22. A calcium channel $\alpha_2\delta$ subunit according to claim 20 or 21 characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 4, SEQ ID N° 5 or SEQ ID N° 6.

23. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20 to 22 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 340 and amino acid number 1062 of SEQ ID N°20.

24. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 20 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°22.

25. A calcium channel $\alpha_2\delta$ subunit according to claim 20 or 24 characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 10, SEQ ID N° 11 or SEQ ID N° 12.

26. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20, 24 or 25 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 306 and amino acid number 1019 of SEQ ID N°20.